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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/427,873	10/27/1999	MICHAEL R. BOYD	175912	3870

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LEYDIG VOIT & MAYER LTD
TWO PRUDENTIAL PLAZA
SUITE 4900
180 NORTH STETSON
CHICAGO, IL 606016780

EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/427,873	BOYD, MICHAEL R.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE f this c mmunication appears on the cover sheet with the corresp ndenc address --

P riod f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November, 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Response to Amendment

Status of the Claims

1. Acknowledgement is hereby made of receipt and entry of the amendment received 06 November, 2002, wherein claims 20 and 22 were amended and new claims 28-31 submitted. Claims 20-31 are currently under consideration.

35 U.S.C. § 112, First Paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 22-31 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. The issue raised in this application is whether the original application provides adequate support for claims involving the coadministration of CV-N and a virus or viral envelope glycoprotein. An applicant shows possession of the claimed

invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant

was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure form the mere recitation of function and minimal structure is highly unlikely. In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

The disclosure describes the cloning and sequencing of a novel CV-N having SEQ ID NO.: 2. The antiviral activity, as it pertains to HIV-1, of this compound was assessed in a simple *in vitro* tissue culture assay (see Example 5). The disclosure states that an object of the present invention is to "provide antiviral proteins and peptides" (see p. 3, second ¶) and to provide a "pharmaceutical composition, which inhibits the growth or replication of a virus,

such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-1 or HIV-2" (see p. 3, fourth ¶). The disclosure also indicates that CV-N can be administered concomitantly with another antiviral compound (e.g., AZT) (see p. 26, second ¶). Various formulations are also disclosed. However, at no point does the disclosure describe the preparation of a pharmaceutical composition comprising CV-N and a retroviral envelope glycoprotein, particularly HIV-1 gp120. This is not surprising, considering that CV-N appears to exert its antiviral activity by binding to the viral envelope and disrupting virion-receptor binding interactions. Thus, the skilled artisan would surmise that a composition comprising both ingredients would lead to CV-N/gp120 binding in the sample thereby essentially neutralizing the antiviral activity of CV-N. Therefore, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention at the time of filing.

4. Claims 20-31 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed toward methods of inhibiting enveloped virus binding to a cell target in a host, through the administration of a CV-N antiviral protein, peptide, or conjugate thereof, having the amino acid sequence of SEQ ID NO.: 2, or an antiviral fragment thereof comprising at least nine contiguous amino acids. The disclosure teaches that CV-N is a single 101 amino acid protein containing two intrachain disulfide bonds. The protein fails to display any significant sequence homology to other known proteins. It appears that CV-N binds directly to HIV-1 gp120. Other limitations specify that a viral envelope glycoprotein may also be coadministered with the antiviral peptide of interest. Applicant further indicates

(see p. 4, specification) that "yet another object of the present invention is to provide a method of treating an animal, in particular a human, infected by a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-2 [sic-HIV-1] or HIV-2. A related object of the present invention is to provide a method of treating an animal, in particular a human, to prevent infection by a virus, such as a retrovirus, in particular a human immunodeficiency virus, specifically HIV-1 or HIV-2." The disclosure fails to provide any data suggesting that the claimed compositions would function in an in vivo setting. However, the specification does demonstrate that CV-N administration in the absence of a viral envelope glycoprotein, results in inhibition of HIV-1 viral replication in an *in vitro* tissue culture assay. Appropriately drafted claim language, as supported by the disclosure, directed toward this embodiment would be acceptable (i.e., An *in vitro* method of inhibiting enveloped virus binding to a cell target ... by administering a CV-N protein having SEQ ID NO: 2 ...). The disclosure is not enabled for in vivo inhibitory applications, particularly with respect to HIV-1 and -2.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to

provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure clearly fails to provide sufficient guidance pertaining to the molecular determinants modulating the antiviral activity of SEQ ID NO.: 2. Thus, the specification fails to teach which nine contiguous amino acids will display the requisite antiviral activity. Applicant argues that only routine experimentation would be required to ascertain which peptides will work. The Examiner does not concur with this assessment. It has been well-documented in the prior art that single amino acid additions, substitutions, or deletions can have deleterious effects on the activity of any given protein or peptide. Clearly the applicant does not understand which regions of CV-N are required for the antiviral activity. Applicant is reminded that the claims encompass any nine contiguous amino acid stretch of CV-N. It could include a protein with a single amino acid deletion or a polypeptide consisting of only nine amino acids. However, the disclosure fails to direct the skilled artisan toward any particular region of the CV-N molecule that is *sine qua non* for antiviral activity. Thus, the skilled artisan would be required to synthesize and screen an inordinate number of peptides. Applicants additionally argue that the declarations provided 06 August, 2001, and 05 February, 2002 (paper nos. 7-1, 7-2, and 10), provide support for the claimed invention. These declarations describe the preparation of a small number (three) of CV-N mutants. Specifically, Pro51Gly, Asn30Gln/Pro51Gly, and Pro51Gly:Asn30Gln/Pro51Gly:Ala71Thr mutants were generated and their *in vitro* antiviral activities assessed. The CV-N protein is 101 amino acids in length. The declaration fails to identify those molecular determinants that modulate the antiviral activity of the compound. Which nine contiguous amino acids will retain the desired activity. The declaration does not address this concern

and represents a rudimentary attempt to begin addressing this problem.

2) The prior art teaches that the development of HIV-1 antivirals, as well as other antivirals, has been a largely unsuccessful endeavor (Domingo *et al.*, 1985; Öberg and Vrang, 1990; Saunders, 1992; Yarchoan and Broder, 1992; Ramachandran *et al.*, 1994; Gait and Karn, 1995; and Richman, 1996) due to a number of factors such as the lack of suitable animal models and the quasispecies nature of HIV. Applicant suggests that the Office has failed to provide any scientific evidence that questions the validity of the *in vitro* screening assay employed. Applicant is again directed toward the references relied upon, which have yet to be adequately addressed. Saunders (1992) reviewed the state-of-the-art pertaining to five novel antivirals that were rushed into Phase-II clinical trials. The results were unanimously discouraging. The author reported (p. 262) that "Initial studies with TIBO showed no toxicity but also **no definite evidence of efficacy despite achieving plasma levels well above the IC_{50} values.**" Concerning other compounds (e.g., BI-RG-587, L697661, U-87201), the author concluded that "**there are still no reports describing efficacy as measured by the usual markers in human ... On the contrary, the initial findings are somewhat pessimistic given that the most consistent observation is one of rapid resistance.**" Thus, the current compounds, all of which received considerable *in vitro* testing before preceding to Phase-II clinical trials, all failed to display any clinical efficacy. Concerning various *in vitro* and *in vivo* antiviral screening assays, Öberg and Vrang (1990) reported (see p. 466, abstract) that "**The relevance of the different screening methods for predicting clinical efficacy is at present uncertain due to the low number of compounds that have been evaluated in double-blind placebo-controlled clinical trials.**" The authors specifically address some of the limitations of tissue culture-based screening assays and

note that cell types that reflect the natural *in vivo* target of HIV-1 should be employed (e.g., PBMCs, monocytes, macrophages), as well as, different patient isolates (see p. 469, left col.). Applicants failed to perform these activities in their own screening assay. The authors also noted a number of disadvantages pertaining to animal models as well (see p. 469, right col.). For instance, concerning murine models, the authors state that "... **murine metabolism seem likely to differ too much from ... human metabolism to make these systems useful** (26)." Richman (1996) notes that HIV-1 and -2 exist as a *quasispecies* in the infected patient. Thus, any given patient already has a large number drug-resistant variants circulating within them. Application of any given antiviral simply selects for these variants which explains why drug failure is so problematic.

Gait and Karn (1995) also summarize a number of problems associated with antiviral development as follows (p. 437, Conclusions):

> There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. **All of the protease inhibitors that have entered clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivities for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor bioavailability and rapid clearance.** As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as **sequestration of the drug by serum proteins, drug resistance** and **uneven distribution throughout the body.** Since **these types of problems are unpredictable,** it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage. ... Much hard work (and perhaps a little luck) will be needed before safe and effective anti-HIV drugs become available.

Thus, another publication illustrates that simple *in vitro* tissue

culture assays can not be relied upon to predict antiviral clinical efficacy. Ramachandran and colleagues (1994) reviewed the results of a phase-I clinical trial involving a fusion protein (CD4-PE40) having a high affinity for HIV-1 gp120. This compound inhibits viral binding and internalization *in vitro*. However, a different picture emerged from the clinic wherein it was reported (see p. 1012, last paragraph) that "**Plasma RNA and proviral DNA measurements in serial samples after multiple infusions of CD4-PE40 showed that virus load in the blood remained stable, with little variation. These findings demonstrate that the levels of CD4-PE40 achieved, even at the maximum tolerated dose, are inadequate to reduce virus replication.**" Yarchoan and Broder (1992) also reviewed the utility of in vitro screening assays for assessing clinical development. The authors were particularly interested in compounds that inhibit viral binding and internalization, the same step targeted by the claimed CV-N peptides. The authors reported (see p. 99, abstract) that "**while a number of agents have been found to block viral binding to the target cell *in vitro*, these agents have generally not shown clear-cut evidence of clinical activity.**" The authors stated that this failure could be attributed to several factors such as the failure of these compounds to penetrate solid lymphoid organs, their failure to inhibit cell-cell viral transmission, and serum protein binding which precludes the compound from reaching the target site. The authors conclude (p. 104, third paragraph) that "**the results with these drugs do serve as a reminder that the identification of activity of agents *in vitro* is not a guarantee of clinical activity.**" Thus, the skilled artisan would be reasonably skeptical of any antiviral data that was obtained solely from an *in vitro* tissue culture assay.

Applicant continues to argue that the specification fully enables the claimed invention. It was argued that the *in vitro*

assay relied upon is widely accepted as being predictive of *in vivo* and clinical results. Contrary to applicant's assertion, the *in vitro* assay relied upon is clearly not a reliable predictor of clinical efficacy. It has been well-documented that simple *in vitro* screening assays are not predictive of clinical efficacy (Domingo *et al.*, 1985; Öberg and Vrang, 1990; Saunders, 1992; Yarchoan and Broder, 1992; Ramachandran *et al.*, 1994; Gait and Karn, 1995; and Richman, 1996). The rational design of antivirals is a difficult process. Random *in vitro* drug screening assays are only a rudimentary first step in the identification of efficacious antiviral agents. Accordingly, the results obtained from this assay do not constitute an appropriate working embodiment. Applicant also argues that the declarations relied upon provide further evidence that the claimed invention is enabled. One of the declarations (paper no. 10) references an Ebola virus murine model of infection. While these results are promising, they fail to address any critical parameters that are used to assess the putative efficacy of an HIV antiviral such as reductions in viral load or increases in $CD4^+$-lymphocyte count. Thus, the skilled artisan can not make any direct extrapolations from the Ebola virus-murine model data. The other declarations (paper nos. 7-1 and -2) fail to provide any data that would lead the skilled artisan to conclude that CV-N, or nine contiguous amino acids thereof, is efficient at combating HIV-1 infection *in vivo*.

3) It was previously argued that the disclosure failed to provide a sufficient number of working embodiments that would enable the full breadth of the claimed invention. Applicant contends that the specification is fully enabling and notes that data was obtained from a macaque model. Applicant provided an earlier declaration (05 February, 2001) under 37 C.F.R. § 1.132 involving data obtained from an SIV model. A gel comprising CV-N was applied intrarectally or intravaginally and an inoculant comprising the virus SHIV89.6P

administered. This experiment fails to reproduce those characteristics that are most likely to be present in human infection. One of the embodiments of the claimed invention is to inhibit viral infectivity in a host. This experiment does not address the ability of CV-N to reduce the viral burden and increase the $CD4^+$-lymphocyte count in HIV-1-infected patients, particularly those with a high viral load. While CV-N might be useful as a prophylactic when administered in a specific form prior to sexual intercourse, the claims are not limited to such a finding. The declaration also failed to address a number of other important issues. For instance, the declaration was silent pertaining to challenge studies involving different HIV-1 and -2 isolates, as well as, other viral isolates (i.e., FIV, BIV, EIAV, CAEV, HSV, CMV, HTLV, etc.). Insufficient guidance was provided concerning the ability of CV-N to inactivate physiologically relevant concentrations of HIV-1, HIV-2, or other viruses. The declaration was also silent pertaining to the pharmacological and therapeutic profile of CV-N. The experimental model employed failed to measure reductions in viral load. It has been well-documented that HIV-1-infected patients produce upwards of 1×10^{10} virions per day. It seems unlikely that adequate concentrations of the CV-N protein can be maintained over sufficient periods of time to provide any meaningful effect. The experimental model employed did not provide any guidance pertaining to the pharmacological properties of the peptide. Many compounds fail to display clinical efficacy because of pharmacological concerns (i.e., binding and inactivation by serum proteins, rapid clearance rate, poor circulating half-life, inability to target the tissue of interest [i.e., the lymphatic compartment]). However, none of these properties were addressed in the declaration. Thus, the skilled artisan cannot make an meaningful deductions pertaining to the therapeutic properties of the antiviral composition. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly

require undue experimentation from the skilled artisan to practice the claimed invention.

Contrary to applicant's assertion, the declaration provided 30 January, 2002, was adequately addressed. This declaration disclosed the preparation of a small number of CV-N mutants. A series of site-directed mutants (Asn30Ala/Gln/Val, Pro51Gly, Asn30Ala:Pro51Gly, Asn30Gln:Pro51Gly:Ala71Thr) were prepared and their *in vitro* antiviral activities against HIV-1 assessed. Applicant contends that the mutants displayed essentially the same antiviral activity as wildtype CV-N. Perusal of the data indicates that the mutants displayed the same or better activity against three (RoJo, Ba-L, ADA) of the tested isolates, but poorer activity against one (WeJo) of the tested isolates. While this preliminary data is promising, it still fails to clearly identify those molecular determinants modulating the antiviral activity of CV-N. The declarant further argues that by utilizing the three-dimensional structure of CV-N, the skilled artisan could design suitable mutants with the desired activity. Once again, this simply represents an invitation to further undue experimentation since the applicant does not know which molecular determinants are responsible for the antiviral activity of CV-N. Additional data was provided concerning the ability of CV-N to inhibit Ebola virus infection in a murine model. While this data is promising, once again the murine model of infection is hardly predictive of clinical efficacy. Moreover, there is no reason to suspect that this activity would be present against non-enveloped viruses which lack the requisite carbohydrate structures required for binding.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Obviousness-Type Double Patenting

5. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel,* 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum,* 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi,* 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman,* 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

6. Claims 20 and 21 stand **provisionally** rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-24 of copending Application Serial No. 09/428,275. Applicants have indicated that this rejection will be addressed when allowable subject matter has been agreed upon.

Correspondence

7. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be

submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

8. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

08 February, 2003